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High Production Volume Chemical Challenge Program

Robust Summaries and Test Plan for Dicamba and Acifluorfen Intermediates Category

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1.0 Introduction

1.1 Overview

BASF Corporation hereby submits for review and public comment the robust summaries and test plan for the Dicamba and Acifluorfen Intermediates Category of chemicals, under the United States Environmental Protection Agency's (U.S. EPA) High Production Volume (HPV) Chemical Challenge Program. This document addresses nine HPV sponsored chemicals, all of which are intermediates found in the production of dicamba and acifluorfen (see Table 1). Three non-HPV chemicals are used to support the chemical category where data from these chemicals are used for read across. Data read across occurs when physicochemical and toxicological data from one chemical is used for another chemical, and is done only when the two chemicals are deemed sufficiently similar in structure that they are likely to have similar chemical and toxicological properties.

The purpose of this plan is to develop screening level physicochemical data, environmental fate and effects, and mammalian health effects data for the nine HPV chemicals consistent with the Screening Information Data Set (SIDS). Therefore, this plan summarizes the existing SIDS data for the nine HPV sponsored chemicals and makes recommendations for testing to fill any data gaps in the SIDS endpoints. As the U.S. EPA has encouraged the use of chemical categories where scientifically justified to reduce animal testing, a category approach was developed for this plan.

Hefter et. al. (1999) defined a chemical category for the purposes of the HPV program to be a group of substances whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern, as a result of structural similarity. A Dicamba and Acifluorfen Intermediates category was developed for these chemicals based on structural similarities, which uses data read across within a category where scientifically justified to fill data gaps in the SIDS endpoints.

Table 1
Summary of chemicals in the Dicamba and Acifluorfen Intermediates Category.

CAS Number	Name	Remark
1982-69-0	Dicamba, sodium salt (3,6-Dichloro-2-methoxybenzoic acid, sodium salt)	HPV
68938-79-4	3,6-Dichloro-2-hydroxybenzoic acid, potassium sodium salt	HPV
68938-80-7	3,6-Dichloro-2-hydroxybenzoic acid, dipotassium salt	HPV
583-78-8	2,5-Dichlorophenol	HPV
52166-72-0	2,5-Dichlorophenol, sodium salt	HPV
68938-81-8	2,5-Dichlorophenol, potassium salt	HPV
1984-58-3	2,5-Dichloroanisole	HPV
63734-62-3	Benzoic acid, 3-[2-chloro-4-(trifluoromethyl)phenoxy]	HPV
72252-48-3	Benzoic acid, 3-[2-chloro-4-(trifluoromethyl)phenoxy], potassium salt-	HPV
1918-00-9	Dicamba (3,6-dichloro-2-methoxybenzoic acid)	Supporting
50594-66-6	Acifluorfen	Supporting
62476-59-9	Acifluorfen, sodium salt	Supporting

HPV = Chemical sponsored by BASF Corporation under the U.S. EPA HPV program.
Supporting = Chemical that is physicochemically and/or toxicologically similar, and is used to support the chemical category.

1.2 Methods for Data Review of SIDS Endpoints

A review of the scientific literature and BASF Corporation's company data was conducted on the physicochemical properties, environmental fate and effects, and mammalian toxicity endpoints for the twelve chemicals in the Dicamba and Acifluorfen Intermediates category. Searches were conducted using CAS numbers and chemical names using the following databases: TOXLINE, ECOTOX, MEDLINE, and CHEMID. Standard handbooks and databases (e.g CRC Handbook on Chemicals, IUCLID, Merck Index, etc.) were consulted for physicochemical properties. Over 118 individual studies, reports and other data sources were reviewed in development of this test plan, and the literature citations for all of these sources are included in Appendix A.

In accordance with U.S. EPA guidance, in those instances where measured physicochemical parameters and environmental fate data were not available, these properties were developed using EPIWIN (version 3.05) modeling. EPIWIN is an acronym for the Estimation Programs Interface for Microsoft Windows 3.1 (June 1998), and is a package of computer programs developed by the U.S. EPA Office of Pollution Prevention and Toxics that uses computational methods and structure-activity relationships (SAR) in estimating chemical properties, environmental fate and aquatic toxicity of organic chemicals. Due to the inherent limitations of SAR approaches, EPIWIN modeling may produce non-realistic estimates; therefore, EPIWIN data are evaluated for reasonableness prior to use.

In accordance with the U.S. EPA guideline, environmental fate and transport estimates were developed using the level III equilibrium criteria model (EQC) version 1.01 as described in Mackay et.at. (1996). The environmental fate and transport of most compounds in the Dicamba and Aciflurofen intermediates category is pH dependent; therefore, EQC modeling was conducted with the form of the test material as indicated in the HPV list to provide an estimate of the distribution of that particular form. .

Lastly, robust summaries were prepared for studies as to provide a detailed summary of the test methods and results. Though several studies may have been evaluated for a particular SIDS endpoint, robust summaries were prepared only for the critical study that represented the best available data. Selection of the critical study was based on a review of all studies using the ranking system developed by Klimisch et al (1997), as well as the criteria outlined in the U.S. EPA's methods for determining the adequacy of existing data.

2.0 Dicamba and Acifluorfen Intermediates Category

2.1 Category Analysis

This plan addresses nine HPV chemicals under the Dicamba and Acifluorfen Intermediates Category, which is comprised of three groups (see Table 2). The substances under evaluation are all intermediates

found in the production of dicamba and acifluorfen, and include the salts and acids of dicamba and acifluorfen. Specific discussions regarding the justification of the categories are presented in Section 3. The chemical categories were developed in accordance with the EPA's recommendation in that substances within each group have physicochemical and/or toxicological properties that are likely to be similar, and follow a regular pattern, as a result of structural similarities. The similarities are based on a common functional group, common precursors or breakdown products (that is, structurally similar chemicals), and an incremental and constant change across the category.

Table 2
Summary of Groups within the Dicamba and Acifluorfen Intermediates Category.

Group 1
Dicamba (3,6-dichloro-2-methoxybenzoic acid) [1918-00-9]
Dicamba, sodium salt (3,6-Dichloro-2-methoxybenzoic acid, sodium salt) [1982-69-0]
3,6-Dichloro-2-hydroxybenzoic acid, potassium sodium salt [68938-79-4]
3,6-Dichloro-2-hydroxybenzoic acid, dipotassium salt [68938-80-7]
Group 2
2,5-Dichlorophenol [583-78-8]
2,5-Dichlorophenol, sodium salt [52166-72-0]
2,5-Dichlorophenol, potassium salt [68938-81-8]
2,5-Dichloroanisole [1984-58-3]
Group 3
Acifluorfen [50594-66-6]
Acifluorfen, sodium salt [62476-59-9]
Benzoic acid, 3-[2-chloro-4-(trifluoromethyl)phenoxy] [63734-62-3]
Benzoic acid, 3-[2-chloro-4-(trifluoromethyl)phenoxy], potassium salt [72252-48-3]

2.2 Salts and Acids

The substances under evaluation are all intermediates found in the production of dicamba and acifluorfen, and include salt and acid forms of the same chemical. The acid and salt forms of the same chemical are expected to have many similar physicochemical and toxicological properties; therefore, data read across is used for those instances where data are available for the acid form but not the salt, and vice versa. This position is based on experimental studies that have clearly demonstrated a high degree of similarity between the toxicokinetics and toxicodynamics of acid and salt forms of the same chemical. In fact, when reviewing the results of a metabolic study with dicamba in rats the U.S. EPA Data Evaluation Record (DER) stated: "Results indicate that there were no significant differences in absorption, distribution, metabolism and excretion among dicamba free acid and its three amine salts." Regarding physicochemical properties and fate, the "read across" method is valid where the original physical form of the material is irrelevant to the endpoint. This would include biodegredation at high dilutions, water

stability at defined pH, and transport/distribution at high dilution. Read across does not apply for other parameters dependent upon bulk physicochemical properties, such as melting point, vapor pressure, boiling point, initial transport/distribution in the environment (conditions near the relevant discharge source), partition coefficient in unbuffered systems and water solubility. Logic and judgment must be used when making assessments about actual systems based on pKa values, pH levels and bulk chemical properties. Mackay et al (1996) states that for Type 5 compounds (substances that can exist as several reversibly interchangeable species, including carboxylic acids) additional work is needed in developing a more general model.

A general premise in regulatory toxicology is that testing an acid form of a chemical is representative of testing that chemical as a salt. Many chemicals are marketed as various salts to enhance water solubility, whereas the toxicology testing is often done the acid form. In the gastrointestinal tract, acids, bases and salts are absorbed in the undissociated (non-ionized) form by simple diffusion (Niesink,et al. 1996, , Klaassen, 1995, Hayes, 1994). In general the amount of dissociation of acids and bases is determined by the pKa (or pKb)- values of the substance and the pH of the environment. The pH of the stomach varies between 1-3 and in the intestines pH values between 5 and 8 are reported (Niesink et al.,1996).

In an acidic environment, acids will be present mainly in the non-ionized form. The amount of dissociation depends on the strength of the acid (reflected by its pKa value) (Klaassen, 1995). Strong acids may be dissociated to some extent in very acidic environment like the stomach, but weaker acids will occur mainly undissociated. Salts may dissociate in an aqueous environment too, forming a cation and an anion. For the compounds under consideration in this document, the anion formed upon dissociation of the salt is the same as the anion resulting from dissociation of the acid. In the acidic environment of the stomach the generated anion (whether generated from the acid or the salt) will accept a proton and hence will be present as the free (undissociated) acid.

Thus, it is expected that both the acids and the salts will be present in (or converted to) the acid form in the stomach. This means that for both types of parent chemical (acid or salt) the same compounds eventually enter the small intestine, where the equilibrium, as a result of increased pH, will shift towards dissociation (ionized form) (Klaassen, 1995). Hence, the situation will be similar for compounds originating from salts and those originating from acids and therefore no differences in uptake are anticipated.

Metabolic studies for dicamba have been performed that demonstrate this position clearly (BASF,1994). For dicamba it was established that both the free acid and its salts showed similar dissociation patterns in water, under both basic and under acidic conditions (BASF, 1993). Five amine salts were tested and each reached equilibrium of essentially 100% dissociation within 75 seconds in water with a reaction half life of less than 10 seconds. It was concluded that dicamba salts readily and quickly dissociate to the dicamba anion in aqueous solutions. An *in vivo* study in male rats with radiolabelled salts of dicamba did not show

any differences between the salts and the free acid on absorption, distribution, metabolism and excretion (BASF, 1994). The U.S. EPA Data Evaluation Record (DER) for this study stated: "Results indicate that there were no significant differences in absorption, distribution, metabolism and excretion among dicamba free acid and its three amine salts. Therefore, these results confirm the Registrant's hypothesis that dicamba, as a free acid or as amine salt form will be rapidly dissociated and absorbed in the animal's digestive system."

This position is further supported by comparative toxicology results from studies conducted with the acid and the salts of dicamba. Rat oral LD50 values are very similar between the acid and five salts varying between 1352 and 1870 mg/kg-bw. Other acute tests demonstrated similar dermal and inhalation toxicity as well as eye and skin irritation and skin sensitization. Genotoxicity tests conducted with the acid and three amine salts all demonstrated negative results for *in vitro* mutagenicity and *in vitro* and *in vivo* chromosome aberration.

For the other compounds there are no specific comparison studies of salts and acid. However, based on structural considerations (that is, absence of a carboxylic acid group or the positioning of electron withdrawing substituents further away from the carboxylic acid group) both 2,5-dichlorophenol and benzoic acid, 3-[2-chloro-4-(trifluoromethyl)phenoxy] are expected to be weaker acids than dicamba. For weaker acids, it is expected that the relative amount of non-ionized acid present in the stomach will be even higher and that the situation after administration of the salt will resemble the situation after administration of the acid even more so than with dicamba. For acifluorfen, the toxicology database was developed using the sodium salt and this is the form of the molecule that is isolated in the manufacturing process.

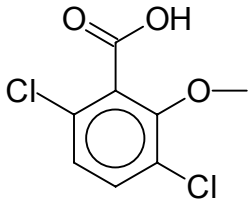
Based on these considerations it is concluded that uptake will not differ for acids and salts in the different categories, and the toxicology is expected to be the same. Therefore, data read across is used for those instances where data is available for the acid form but not the salt, and vice versa.

3.0 Categorization

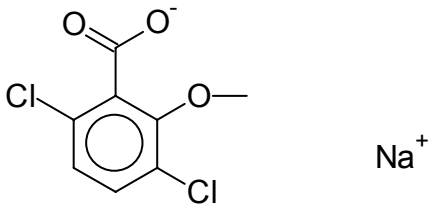
3.1 Group I

3.1.1 Chemistry

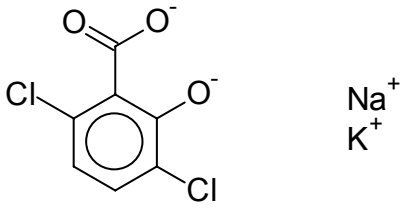
1. CAS 1918-00-9: Dicamba (3,6-dichloro-2-methoxybenzoic acid)



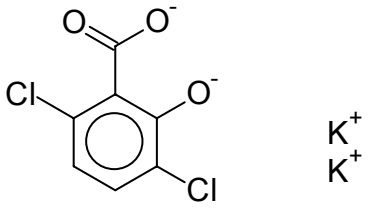
2. CAS 1982-69-0: Dicamba, sodium salt (3,6-Dichloro-2-methoxybenzoic acid, sodium salt)



3. CAS 68938-79-4: 3,6-Dichloro-2-hydroxybenzoic acid, potassium sodium salt



4. CAS 68938-80-7: 3,6-Dichloro-2-hydroxybenzoic acid, dipotassium salt



Group I is comprised of dicamba, its sodium salt and three of its intermediates. All chemicals in this group have in common that the central part of the structure consists of a phenyl moiety containing two

chlorine atoms in para- position to each other. No difference in chemical behavior is therefore expected based on this part of the structure. Furthermore, all chemicals in Group I bear an oxygen atom that is directly attached to the phenyl ring. This oxygen atom is present either as part of a methoxyl group (chemicals 1 and 2) or a functionalized hydroxyl group (chemicals 3 and 4). Also, Group I chemicals contain a carboxylate moiety on the phenyl ring that is present as free carboxylic acid (chemical 1) or as sodium or potassium carboxylate (chemicals 2, 3, 4). The basis for the grouping of dicamba and its intermediate chemicals in Group I is the presence of this carboxylate moiety.

The carboxylate group is an electron withdrawing substituent and a mildly deactivating group (that is, deactivating the phenyl ring towards electrophilic aromatic substitution). In addition, halobenzenes that have such an electron withdrawing substituent in the ortho- or para- position relative to the halogen atom can undergo nucleophilic aromatic substitution. The appearance of the carboxylate group, in both the free carboxylic acid or carboxylate salt, does not influence these characteristics.

The different appearance of the oxygen atom as a methoxyl or hydroxyl group attached to the phenyl ring is not predicted to have a significant influence on the reactivity of the chemical. Both hydroxyl and methoxyl substituents are strongly activating ortho- and para-directors (that is, activating the phenyl ring towards electrophilic aromatic substitution). They activate the phenyl ring by resonance donation of oxygen pi atoms, and for this it does not matter whether the oxygen is present as free or functionalized hydroxyl group or as part of the methoxyl group. Hence, the chemicals in Group I are expected to have equivalent chemical reactivity regardless of whether they contain a methoxyl or hydroxyl moiety.

3.1.2 Toxicokinetics and Toxicodynamics

Group I chemicals consist of 3,6-dichloro benzoic acid and three mono- or di-salts of 3,6-dichloro benzoic acid. Based on toxicokintetic studies both the salt forms and the acid form were found to have equivalent absorption from the gastrointestinal tract and other toxicokinetic processes, such as tissue distribution and systemic clearance (Caux et al., 1993, BASF, 1994). Again, the U.S. EPA Data Evaluation Record (DER) for this study stated: “Results indicate that there were no significant differences in absorption, distribution, metabolism and excretion among dicamba free acid and its three amine salts. In other related studies, dicamba is reported to be readily absorbed and excreted. In dairy cows 90% was excreted within 6 hours as the parent compound (72%) and an unidentified metabolite (18%) (Caux et al., 1993, Costa, 1997).

All the chemicals in Group I are expected to have similar biotransformation pathways and elimination rates due to the presence of the carboxyl group, which is expected to be the primary site for conjugation. In a study by Caux et al. (1993) the half-life of dicamba was reported to be 0.4 hours after dermal administration to rats. Demethylation is known to be a route of bacterial degradation of dicamba and cytochrome P450 oxidations in mammals are anticipated to lead to demethylation. In either case,

dicamba and its salt are converted partially to 3,6-dichlorosalicylic acid. The elimination of the chemicals with the methoxyl group may be slower than that of the hydroxyl moiety containing ones, but no significant difference in overall toxicity is expected. Furthermore, the sodium and/or potassium cation should not affect toxicity, since the sodium and potassium cations will be added to the large pools present in the body.

3.1.3 Group I - Testing Rational

Four chemicals were placed into Group I because structurally they are all highly related. They all have a phenyl moiety containing two chlorine atoms in para- position to each other, and contain a carboxylate moiety on the phenyl ring. A summary of proposed testing for this group is shown in Table 3 and completed SIDS data matrix is provided in Section 4. An extensive battery of toxicology testing has been conducted on dicamba, many under Good Laboratory Practices (GLP); therefore, data for the SIDS toxicity endpoints for this group are covered mostly by data read across from dicamba. Additional mammalian toxicity studies and EPIWIN estimates for physicochemical data support data read across.

Physicochemical Properties

Measured data for melting point, vapor pressure, and water solubility are available for dicamba, while the boiling point and partition coefficient were predicted with the EPIWIN modeling. EPIWIN modeling for chemicals 2-4 was also conducted. It must also be remembered that some of these parameters are highly pH dependent when ionizable groups are included. For the needs of the HPV Program, estimation and read across provide sufficiently reliable information and no further physicochemical testing is recommended for Group I.

Environmental Fate

Environmental fate data from Group I was developed using both measured and EPIWIN model results for dicamba,and the other members of the group. Dicamba's $t_{1/2}$ for photodegradation in water was found to be 50 days, and in a hydrolysis test it was found to be stable in water. Read across is appropriate for primary photodegradation in water for all other group members, but indirect photodegradation in air was calculated for all members using EPIWIN. Based on the EQC Level III model, it is predicted that dicamba will be distributed to soil (70%) and water (29.9%) under conditions of equal emission to water, soil and air. There is clear evidence that biodegradation will occur for all members of Group I; however, it is not known if any member can be considered readily biodegradable by the OECD criteria. Therefore, a biodegradation study of dicamba is recommended.

Ecotoxicity

Acute fish, daphnia and algae inhibition studies were conducted for dicamba, with data available for both freshwater and saltwater species. Dicamba has a moderate acute ecotoxicity with a 96-hr LC50 = 117 mg/L for *Cyprinodon variegatus*, a 120-hr EC50 > 3.7 mg/L for algae and a daphnia 48-hr LC50 >100 mg/L. Based on the high degree of structural similarity between the chemicals in Group I, testing for dicamba adequately covers the SIDS ecotoxicity endpoints for the other Group I chemicals and no further testing is warranted.

Mammalian Toxicity

A robust set of mammalian toxicity data was located for Group I chemicals, including several acute toxicity tests via the oral, dermal and inhalation routes of administration and a multigenerational reproduction/developmental test. Data are available for dicamba and dicamba, sodium salt and the results support the chemical categorization and data read across.

The data indicate the chemicals in Group I have a low acute toxicity via the oral, dermal and inhalation routes of exposure. Dicamba had the following acute toxicities: rat, oral LD50 = 1707 mg/kg; rabbit, dermal LD50 >1716 mg/kg; and rat, inhalation LC50 > 8200 mg/m^3. For dicamba, sodium salt the rat, oral LD50 > 1000 mg/kg and rabbit, dermal LD50 > 2000 mg/kg. The similarity in acute toxicity values between dicamba and dicamba, sodium salt further support the Group I categorization and the position that acid and salt forms will have equivalent toxicities.

The data also showed that dicamba is not expected to demonstrate genetic toxicity, as it was negative in both *in vitro* and *in vivo* genotoxicity studies. It was negative in an Ames assay in four strains (TA98, TA100, TA1535 and TA1537) with and without metabolic activation, negative in an *in vitro* chromosomal aberration assay in Chinese hamster ovary (CHO) cells, and negative in an *in vivo* micronucleus test in mice.

In a 21-week dietary study, male and female rats were exposed to 1000, 5000 and 10000 ppm dicamba, resulting in dose levels of 69.4, 342 and 682 mg/kg-bw for males and 79.5, 392 and 751 mg/kg-bw for females. Overall, the results showed a NOAEL = 342 mg/kg-bw based on effects on body weight, food consumption and elevated alkaline phosphatase (ALP) levels.

For developmental toxicity and toxicity to reproduction, a robust set of studies was available for dicamba, which included multigenerational studies in rats and teratogenicity studies in rats and rabbits. The results indicate the chemicals in Group I have a low developmental and reproductive toxicity, and are not teratogenic. In a 2-generation study, rats were exposed to dicamba at concentrations of 500, 1500 and 5000 ppm in the diet. Results indicated a parental NOAEL = 1500 ppm based on decreased female body weight gain during pregnancy and increased liver weights in both sexes, and a developmental NOAEL = 500 ppm based on slightly reduced growth of F2-pups. No teratogenic effects were seen in either rats or

rabbits during gestational day (GD) exposure studies. In one study, rats were exposed to dicamba via oral gavage on GD 6-19 at doses of 64, 160 and 400 mg/kg-bw. The maternal NOAEL = 160 mg/kg-bw based on decreased body weights, food consumption and clinical symptoms while the teratogenicity NOAEL > 400 mg/kg-bw based on the absence of any significantly increased malformations or variations. In the second study, pregnant rabbits were exposed to dicamba on GD 6-18, to doses of 30, 50 and 300 mg/kg-bw. Results indicated the maternal NOAEL = 30 mg/kg-bw based on loss of pregnancy and clinical signs, while the teratogenicity NOAEL > 300 mg/kg-bw based on the absence of any significantly increased malformations or variations.

Overall, the SIDS data set for mammalian toxicity data is robust and it is concluded that no further mammalian toxicity testing is warranted for Group I.

Table 3
Summary of Data Gap Analysis for Group I

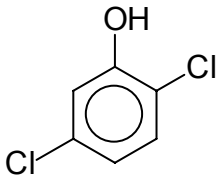
SIDS Level I Endpoint	Dicamba (1918-00-9)	Dicamba, sodium salt (1982-69-0)	3,6-Dichloro-2-hydroxybenzoic acid, potassium sodium salt (68938-79-4)	3,6-Dichloro-2-hydroxybenzoic acid, dipotassium salt (68938-80-7)
Physicochemical Properties				
Melting point (°C)	A	A	A	A
Boiling point (°C)	A	NA[1]	NA[1]	NA[1]
Vapor pressure (hPa)	A	A	A	A
Partition coefficient (Kow)	A	A	A	A
Water Solubility (mg/L)	A	A	A	A
Environmental Fate				
1° Photodegradation(days)	A	R	R	R
Hydrolysis	A	A	A	A
Fugactiy	A	A	A	A
Biodegradability	T	R	R	R
Ecotoxicity				
Acute Fish (mg/L)	A	R	R	R
Acute daphnia (mg/L)	A	R	R	R
Algal Inhibition (mg/L)	A	R	R	R
Mammalian Toxicity				
Acute Mammalian (mg/kg)	A	A	R	R
Gene Tox – Mutagenicity	A	R	R	R
Gene Tox – Clastogenic	A	R	R	R
Repeat Dose	A	R	R	R
Repro or Development	A	R	R	R

A = Adequate Data Exists, R = Read Across, T = Testing Proposed, NA = Not Applicable
1. These compounds decompose rather than boil.

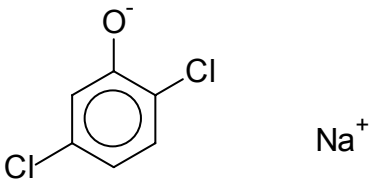
3.2 Group II

3.2.1 Chemistry

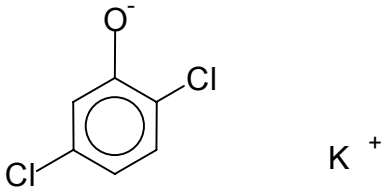
5. CAS 583-78-8: 2,5-Dichlorophenol



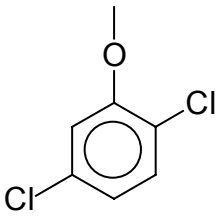
6. CAS 52166-72-0: 2,5-Dichlorophenol, sodium salt



7. CAS 68938-81-8: 2,5-Dichlorophenol, potassium salt



8. CAS 1984-58-3: 2,5-Dichloroanisole



The chemicals in Group II consist of 2,5-dichlorophenol, two of its salts and an intermediate. These chemicals are similar to those in Group I in that the central part of the structure all the Group II chemicals have a phenyl moiety containing two chlorine atoms in para- position to each other. Furthermore, all chemicals in Group II bear an oxygen atom that is directly attached to the phenyl ring. This oxygen atom is present either as part of a methoxyl group (chemical 8) or a functionalized (chemical 6 and 7) or free hydroxyl group (chemical 5).

The different functionlization of the oxygen atom as a methoxyl or hydroxyl group attached to the phenyl ring is not predicted to have a significant influence on the carbon ring reactivity of the chemical. Both hydroxyl and methoxyl substituents are strongly activating ortho- and para-directors (that is, activating the phenyl ring towards electrophilic aromatic substitution). They activate the phenyl ring by resonance donation of oxygen pi atoms, and for this it does not matter whether the oxygen is present as free or functionalized hydroxyl group or as part of the methoxyl group. Hence, the chemicals in Group II are expected to have equivalent chemical reactivity regardless of whether they contain a methoxyl or hydroxyl moiety.

Although there are differences in the chemical reactivity of hydroxyl versus methoxyl groups, a common metabolite arises during biotransformation; therefore, similar toxicity is expected for all members of the group.

3.2.2 Toxicokinetics and Toxicodynamics

Group II chemicals consist of 2,5-dichloroanisole, 2,5-dichlorophenol and its sodium and potassium salt. All the chemicals in Group II are expected to have similar biotransformation pathways and elimination rates due to the high degree of structural similarity. The salt forms and the covalent forms are expected to have similar absorption from the gastrointestinal tract and other toxicokinetic processes, such as tissue distribution and systemic clearance (Caux et al., 1993, BASF,1994).

Studies have shown that the highest concentrations of dichlorophenols are found in liver, kidney and/or spleen, with peak levels occurring 15 minutes after administration (Sloff, et al.,1991, WHO, 1989). 2,5-Dichlorophenol and its salts will be subjected to direct conjugation of the hydroxyl-group with glucuronide or sulfate and will be eliminated quickly from the body via urine (Sloff, et al.,1991, WHO, 1989). 2,5-Dichloroanisole, however, contains a methoxyl-group and demethylation of the methoxyl group, or hydroxylation of the benzene ring, will occur prior to conjugation and concomitant elimination. No significant difference in overall toxicity is expected, although elimination from the body may be slower as compared to 2,5-dichlorophenol and its salts,

3.2.3 Group II - Testing Rational

Four chemicals were placed into Group II because they are all highly related structurally. They all have a phenyl moiety containing two chlorine atoms in para- position to each other, and contain an oxygen atom that is directly attached to the phenyl ring as part of a methoxyl group or hydroxyl group.

A summary of proposed testing for this group is shown in Table 4 and completed SIDS data matrix is provided in Section 4. 2,5-Dichlorophenol has been extensively tested, including several studies under GLP; therefore, health-effects data for the SIDS endpoints for this group are covered mostly by data read across from this chemical. Additional mammalian toxicity studies and EPWIN estimates for physicochemical data support data read across.

Physicochemical Properties

Measured data on melting point, boiling point, and water solubility are available for 2,5-dichlorophenol, while the vapor pressure and partition coefficient were predicted with EPIWIN. To evaluate the accuracy of the EPIWIN estimates, modeling was done for the parameters for which measured data was available and the modeled data was compared to the measured data. The measured data for 2,5-dichlorophenol are in good agreement with the EPIWIN predictions (the measured data and EPIWIN predictions for melting point and boiling point were 59°C and 47°C, and 211°C and 234°C, respectively).

EPIWIN modeling was also performed for 2,5-dichloroanisole to obtain estimates of physicochemical parameters. The results further support the Group II categorization as the values calculated for 2,5-dichloroanisole are in good agreement with those values for 2,5-dichlorophenol, both measured and EPIWIN predicted. Based on a review of the data, and the chemical categorization approach, sufficient data on SIDS endpoints for physicochemical parameters is available and no further testing is warranted for Group II.

Environmental Fate

Experimental data were available for the biodegradation of 2,5-dichlorophenol, and all other environmental fate data from Group II was developed using the EPIWIN model. Good agreement in the model data is seen as with the physicochemical data; however, additional testing is recommended to strengthen the biodegradation endpoint. Therefore, a biodegradation study with 2,5-dichloroanisole is recommended.

Ecotoxicity

At present, no ecotoxicity data for the SIDS endpoints are available for any of the chemicals in Group II. Testing for the ecotoxicity endpoints is, therefore, recommended for filling the requirements of the HPV Program. . Although predictions with the EPIWIN model are possible for the ecotoxicity endpoints, they

are considered most reliable when used to support actual data. Based on the absence of measured data, acute fish, daphnia and algae tests with 2,5-dichloroanisole are recommended

Mammalian Toxicity

Data for mammalian toxicity are available for both 2,5-dichlorophenol and 2,5-dichloroanisole and even though the results support the chemical categorization and data read across for most SIDS endpoints, additional testing for toxicity to reproduction is considered necessary. Both chemicals showed low acute toxicity via the oral, dermal and inhalation routes of exposure. 2,5-Dichlorophenol had the following acute toxicities: rat, oral LD50 = 2475 mg/kg; rabbit, dermal LD50 >8000 mg/kg and rat, inhalation LC50 185000 mg/m^3. For 2,5-dichloroanisole the rat, oral LD50 = 2089 mg/kg and rat, inhalation LC50 = 93000 mg/m^3. Once again there was good agreement in the measured data, which supports the chemical categorization and data read across.

Toxicity test data are available for 2,5-dichlorophenol that demonstrate it does not cause genetic toxicity. It was negative in an *in vitro* gene mutation test assay (OECD 476) using hypoxanthine-guanine phosphoribosyl transferease (HGPRT) loci and was negative in an *in vivo* chromosomal aberration study in mice.

There are sufficient studies that evaluate the sub-chronic toxicity of the chemicals in this Group because two repeated dose studies are available for 2,5-dichlorophenol. In a 21-day test male and female rabbits were exposed dermally to 2,5-dichlorophenol 5 days/week, 6 hours/day to 1, 10 and 100 mg/kg-bw. The results indicate a NOAEL = 100 mg/kg-bw based on localized skin effects. In a 28-day inhalation test, male and female rats were exposed to 2,5-dichlorophenol 5 days/week, 6 hours/day at concentrations of 100, 300 and 1000 mg/m3. In this study a LOAEL = 100 mg/m^3 was reported based on liver effects. These two studies, which cover male and females in two different species and two different routes of administration, are adequately addressing the repeat dose toxicity testing SIDS endpoints for the group.

Neither a toxicity to reproduction nor a developmental study was located for any of the chemicals in Group II, and as such a reproduction/developmental toxicity screening test is planned for 2,5-dichloroanisole.

Overall, based on a review of the existing data for mammalian toxicity and the chemical categorization, it was determined that there is sufficient data for all SIDS endpoints except reproduction and ecotoxicity toxicity. Therefore, a reproduction/developmental toxicity screening test and acute fish, daphnia and algae tests with 2,5-dichloroanisole is warranted.

Table 4
Summary of Data Gap Analysis for Group II

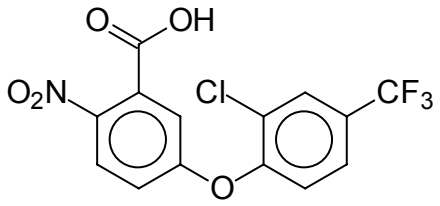
SIDS Level I Endpoint	2,5-Dichlorophenol (583-78-8)	2,5-Dichlorophenol, sodium salt (52166-72-0)	2,5-Dichlorophenol, potassium salt (68938-81-8)	2,5-Dichloroanisole (1984-58-3)
Physicochemical Properties				
Melting point (°C)	A	A	A	A
Boiling point (°C)	A	NA[1]	NA[1]	A
Vapor pressure (hPa)	A	A	A	A
Partition coefficient (Kow)	A	A	A	A
Water Solubility (mg/L)	A	A	A	A
Environmental Fate				
Photodegradation(days)	A	A	A	A
Hydrolysis	A	A	A	A
Fugactiy	A	A	A	A
Biodegradability	A	A	A	T
Ecotoxicity				
Acute Fish (mg/L)	R	R	R	T
Acute daphnia (mg/L)	R	R	R	T
Algal Inhibition (mg/L)	R	R	R	T
Mammalian Toxicity				
Acute Mammalian (mg/kg)	A	R	R	R
Gene Tox – Mutagenicity	A	R	R	R
Gene Tox – Clastogenic	A	R	R	R
Repeat Dose	A	R	R	R
Repro or Development	R	R	R	T

A = Adequate Data Exists, R = Read Across, T = Testing Proposed, NA =Not Applicable
1. These compounds decompose rather than boil.

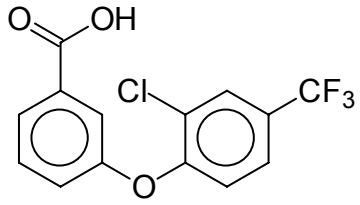
3.3 Group III

3.3.1 Chemistry

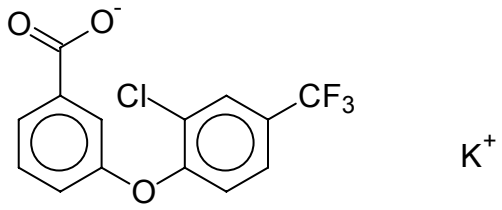
9. CAS 50594-66-6: Acifluorfen



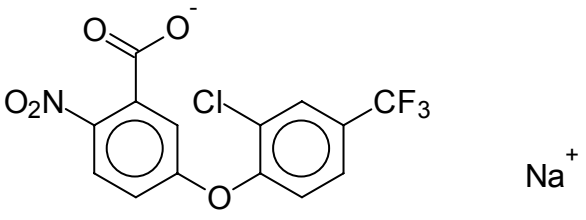
10. CAS 63734-62-3: Benzoic acid, 3-[2-chloro-4-(trifluoromethyl)phenoxy]



11. CAS 72252-48-3: Benzoic acid, 3-[2-chloro-4-(trifluoromethyl)phenoxy], potassium salt



12. CAS 62476-59-9: Acifluorfen, sodium salt



Group III is comprised of acifluorfen, its sodium salt and its two intermediates. As with Groups I and II, there is a high degree of structural similarity between the four chemicals in Group III. All have a basic structure consisting of two phenyl rings connected via an ether moiety, with one phenyl ring bearing a chlorine atom at the 2-position and a trifluoromethyl moiety at the 4-position. The other phenyl ring bears a carboxylate moiety at the 3-position, either in the form of the free carboxylic acid (chemicals 9 and 10) or a carboxylate moiety (chemicals 11 and 12). As with Group I, the appearance of the carboxylate moiety is not expected to significantly influence the chemical reactivity that suggests similar reactivites between all chemicals in the group.

The only difference in structure between acifluorfen and its salt versus its two intermediates is the presence of the nitro group at the 4-position of the phenyl ring, adjacent to the carboxylic acid or carboxylate group. Nitro groups are relatively stable groups. Like the carboxylate moiety, the nitro group is an electron withdrawing substituent and a strongly deactivating group (that is, deactivating the phenyl ring towards electrophilic aromatic substitution). Hence, electrophilic aromatic substitution of acifluorfen is not expected to be an important issue. As stated before, halobenzenes that have an electron withdrawing substituent in the ortho- or para- position relative to the halogen substituent can undergo nucleophilic aromatic substitution. As the nitro group is not in ortho- or para-position to the chlorine atom (it is located on the other phenyl ring) nucleophilic aromatic substitution is also expected to be of little importance. Furthermore, acifluorfen and its sodium salt are predicted to have essentially the same reactivity as previously discussed.

3.3.2 Toxicokinetics and Toxicodynamics

Group III chemicals consist of acifluorfen, its sodium salt and benzoic acid, 3-[2-chloro-4-(trifluoromethyl)phenoxy] and its potassium salt. These chemicals are predicted to have equivalent absorption from the gastrointestinal tract and other toxicokinetic processes, such as tissue distribution and systemic clearance, because these compounds have a high degree of structural similarity and they are acid and salt forms. These chemicals possess halide moieties that may be subjected to reductive dehalogenation catalyzed by cytochrome P450, leading to a radical and an inorganic halide. Acifluorfen and its sodium salt contain a nitro-group, which is absent in the other compounds. This nitro-group may be reduced during phase I biotransformation; a similar reaction is seen with nitrobenzene reduction to aniline. However, this reaction is considered to be of minor significance and all the chemicals in Group III are expected to have similar distribution and rates of elimination.

3.3.3 Group III - Testing Rational

Four chemicals were placed into Group III because structurally they are all highly related. They all have two phenyl rings connected via an ether moiety, with one phenyl ring bearing a chlorine atom at the 2-

position and a trifluoromethyl moiety at the 4-position. The other phenyl ring bears a carboxylate moiety at the 3-position, either in the form of the free carboxylic acid (chemicals 9 and 10) or a carboxylate moiety (chemicals 11 and 12).

A summary of proposed testing for this group is shown in Table 5 and completed SIDS data matrix is provided in Section 4. Acifluorfen, sodium salt has been extensively tested, including several studies under GLP; therefore, data for the SIDS endpoints for this group is covered mostly by data read across from this chemical. Additional mammalian toxicity studies for acifluorfen and benzoic acid, 3-[2-chloro-4-(trifluoromethyl)phenoxy], as well as EPIWIN estimates for physicochemical data, support data read across for this group.

Physicochemical Properties

Measured data are available for the sodium salt of acifluorfen, including melting point, vapor pressure partition coefficient and water solubility, while EPIWIN modeling was used to obtain physicochemical parameters for acifluorfen and the two intermediates. The EPIWIN predictions for acifluorfen were in reasonable agreement with these measured data indicating the validity of the model for this category of compound. Based on a review of the data, and the chemical categorization approach, sufficient data on SIDS endpoints for physicochemical parameters are available and no further testing is warranted for Group III.

Environmental Fate

Both acifluorfen and its sodium salt have measured environmental fate data and EPIWIN modeling was used to fill data gaps. Acifluorfen's $t_{1/2}$ for photodegradation in water was found to be 80-100 hrs, and in a hydrolysis test the acifluorfen, sodium salt was found to be stable in water. Based on the EQC model it is predicted that acifluorfen will be distributed about 85% to soil l and about 15 % to water. Although several studies of biodegradation have been conducted, the results do not allow proper classification; therefore, a biodegradation study of acifluorfen, sodium salt is recommended.

Ecotoxicity

Ecotoxicity data was located for three of the four chemicals in Group III, which included acifluorfen, its sodium salt and benzoic acid, 3-[2-chloro-4-(trifluoromethyl)phenoxy]. All the data showed reasonably good agreement. The fish LC50 values were 2.6 and 17 mg/L for benzoic acid, 3-[2-chloro-4-(trifluoromethyl)phenoxy] and acifluorfen, sodium salt, respectively. In a 120-hr algal inhibition test with acifluorfen, the EC50 >260 mg/L while acifluorfen, sodium salt had LC50 = 77 mg/L in a 48-hr test with *Daphnia magna*. Based on a review of the existing data, and the chemical categorization, it was determined that there is sufficient data for all SIDS ecotoxicity endpoints and that no further testing is warranted.

Mammalian Toxicity

A robust set of mammalian toxicity data was located for Group III, including acute toxicity tests via the oral, dermal and inhalation routes of administration, repeat dose toxicity studies in two species, mutagenicity testing and a multigenerational reproduction/developmental test. Three of the four chemicals in Group III had data available, which included acifluorfen, its sodium salt and benzoic acid, 3-[2-chloro-4-(trifluoromethyl)phenoxy].

Overall, the chemicals in Group III have a low acute mammalian toxicity. For benzoic acid, 3-[2-chloro-4-(trifluoromethyl)phenoxy] the following acute toxicity values were reported: rat, oral LD50 > 50 mg/kg; rabbit, dermal LD50 > 5000 mg/kg and rat, inhalation LC50 > 3400 mg/m^3. Acute mammalian toxicity data for acifluorfen, sodium salt were in good general agreement with the data for benzoic acid, 3-[2-chloro-4-(trifluoromethyl)phenoxy]. For acifluorfen, sodium salt the following acute data were located: rat, oral LD50 = 1540; rabbit, dermal LD50 = 3680; and rat, inhalation LC50 = 6910 mg/m^3.

No mutagenic effects were demonstrated for any of the chemicals in Group III that were tested. Both acifluorfen and benzoic acid, 3-[2-chloro-4-(trifluoromethyl)phenoxy] were negative in Ames tests in four different strains (TA98, TA100, TA1535 and TA1537) with and without metabolic activation, and acifluorfen, sodium salt was found to be negative in both an *in vitro* cytogenetic assay in CHO cells and an *in vivo* cytogenetic assay (OECD 475) in mice.

Two repeat dose toxicity studies were located, and covered both males and females, in two different species and two different routes of administration (oral and inhalation). In a 90-day study male and female Fisher rats were exposed to acifluorfen, sodium salt at dietary concentrations of 0, 20, 80, 320, 1250, 2500, and 5000 ppm, which resulted in dose levels of 1.5, 6.1, 23.7, 92.5, 191.8 and 401.7 mg/kg-bw in males and 1.8, 7.4, 29.7, 116.0, 237.1 and 441.8 mg/kg-bw in females. Results from this study indicated a NOAEL = 320 ppm (23.7 mg/kg-bw) based on the presence of liver effects and damage with concomittant changes in blood chemistry. A NOAEL = 277 mg/kg-bw based on survival and body weight was found in a 21-day dermal study in New Zealand white male and female rabbits exposed to acifluorfen, sodium salt at doses of 92, 277 and 923 mg/kg-bw.

For developmental toxicity and toxicity to reproduction, a robust set of studies were available for acifluorfen, sodium salt that included GLP multigenerational studies in rats and teratogenicity studies in rats and rabbits. The results indicate the chemicals in Group III have a low developmental and reproduction toxicity, and are not teratogenic. In a 2-generation study male and female rats were exposed to acifluorfen, sodium salt at concentrations of 25, 500 and 2500 ppm in the diet. Results indicated a parental NOAEL = 25 ppm (males 1.6 mg/kg-bw; females 2.2 mg/kg-bw) based on an increased incidence of dilated tubules in the outer medulla of the kidney, and a developmental NOAEL =

500 ppm (males 31 mg/kg-bw; females 42 mg/kg-bw) based on reduced pup body weights and an increased incidence of kidney pelvic dilatation.

Two teratogenicity studies were conducted with acifluorfen, sodium salt. In the first study, pregnant female rats were exposed to acifluorfen, sodium salt on GD 6-19, to doses of 20, 90 and 180 mg/kg-bw. Results indicated a parental NOAEL = 20 mg/kg-bw based on decreased body weights and clinical signs such as excessive salivation. For teratogenicity, this study was NOAEL > 180 mg/kg-bw based on the absence of any significantly increased malformations or variations. In the second study, pregnant rabbits were exposed to acifluorfen, sodium salt on GD 6-18, to doses of 3, 12 and 36 mg/kg-bw. Results indicated the parental NOAEL = 12 mg/kg, based on slight inhibition of body weight gain and inhibition of food consumption and teratogenicity NOAEL > 36 mg/kg-bw.

Overall, the SIDS data set for mammalian toxicity data is robust and it is concluded that no further mammalian toxicity testing is warranted for Group III.

Table 5
Summary of Data Gap Analysis for Group III

SIDS Level I Endpoint	Acifluorfen (50594-66-6)	Benzoic acid, 3-[2-chloro-4-(trifluoromethyl)phenoxy] (63734-62-3)	Benzoic acid, 3-[2-chloro-4-(trifluoromethyl)phenoxy], potassium salt (72252-48-3)	Acifluorfen, Sodium salt (62476-59-9)
Physicochemical Properties				
Melting point (°C)	A	A	A	A
Boiling point (°C)	A	NA[1]	NA[1]	NA[1]
Vapor pressure (hPa)	A	A	A	A
Partition coefficient (Kow)	A	A	A	A
Water Solubility (mg/L)	A	A	A	A
Environmental Fate				
Photodegradation(days)	A	A	A	A
Hydrolysis	A	A	A	A
Fugactiy	A	A	A	A
Biodegradability	R	R	R	T
Ecotoxicity				
Acute Fish (mg/L)	R	A	R	A
Acute daphnia (mg/L)	R	R	R	A
Algal Inhibition (mg/L)	A	R	R	R
Mammalian Toxicity				
Acute Mammalian (mg/kg)	R	A	R	A
Gene Tox – Mutagenicity	A	A	R	R
Gene Tox – Clastogenic	R	R	R	A
Repeat Dose	R	R	R	A
Repro or Development	R	R	R	A

A = Adequate Data Exists, R = Read Across, T = Testing Proposed, NA = Not Applicable
1. These compounds decompose rather than boil.

3.4 Test Plan Summary

The following is a summary of the recommended testing for SIDS endpoints.

Group I

A biodegradation study with dicamba according to OECD 301.

Group II

A biodegradation study with 2,5-dichloroanisole according to OECD 301.

An acute fish test with 2,5-dichloroanisole according to OECD 203.

An acute daphnia test with 2,5-dichloroanisole according to OECD 202.

An algae test with 2,5-dichloroanisole according to OECD 201.

A combined repeated dose reproduction study with 2,5-dichloroanisole according to OECD 422.

Group III

A biodegradation study with acifluorfen, sodium salt according to OECD 301.

4.0 SIDS Data Matrix

4.1 SIDS Matrix – Group I

SIDS Endpoint	Dicamba (1918-00-9)		Dicamba, sodium salt (1982-69-0)		3,6-Dichloro-2-hydroxybenzoic acid, potassium sodium salt (68938-79-4)		3,6-Dichloro-2-hydroxybenzoic acid, dipotassium salt (68938-80-7)	
Physicochemical	**Value**	**Comment**	**Value**	**Comment**	**Value**	**Comment**	**Value**	**Comment**
Melting point (°C)	87-108		224	EPIWIN	220	EPIWIN	220	EPIWIN
Boiling point (°C)	329	EPIWIN						
Vapor pressure (hPa)	1.67e-05	Extrapolation	Nil	EPIWIN	Nil	EPIWIN	Nil	EPIWIN
Partition coefficient	0.545	Ionized forml	-0.90	EPIWIN	-4.15	EPIWIN	-4.15	EPIWIN
Water Solubility (g/L)	8.24	OECD 105	150	EPIWIN	1000	EPIWIN	1000	EPIWIN
Environmental fate								
Photodegradation (t1/2 days)	50.3	Direct	50.3	Direct	3.3	EPIWIN	3.3	EPIWIN
Hydrolysis	Stable		Stable		Stable		Stable	
Fugacity	29.9% Soil 70% Water	EQCIII	58.4% Soil 41.4% Water	EQCIII	43.8% Soil 56.1% Water	EQC III	43.8% Soil 56.1% Water	EQC III
Biodegradability	Biodegrades		Biodegrades		Biodegrades		Biodegrades	
Ecotoxicity								
Acute Fish – LD50 (mg/L)	117	*C. variegatus*						
Acute Daphnia – EC50 (mg/L)	>100	*D. magna*						
Algal Inhibition – EC50 (mg/L)	>3.7	*S. capricornutum*						
Mammalian								
Acute – Oral (mg/kg)	1707	Rat	>1000	Rat				
Acute – Dermal (mg/kg)	>1716	Rabbit	>2000	Rabbit				
Acute – Inhalation (mg/m^3)	>8200	Rat						
Gene Tox – Mutagenic	Negative	Ames Assay						
Gene Tox – In-vitro Cytogenetic	Negative	Chrom Aberration						
Gene Tox – In-vivo Cytogenetic	Negative	Micronucleus						
Repeat Dose – 21-Week Rat, Oral NOAEL (mg/kg-bw)	342	Dietary exposure						
Reproduction – 2-Gen Rat, Oral, NOAEL (ppm)	1500 500	Parental and F1 Developmental (F2)						
Developmental – Rat, Oral NOAEL(mg/kg-bw)	160 >400	Maternal Teratogenicity						
Developmental – Rabbit, Oral NOAEL(mg/kg-bw)	30 >300	Maternal Teratogenicity						

4.2 SIDS Matrix – Group II

SIDS Endpoint	2,5-Dichlorophenol (583-78-8)		2,5-Dichlorophenol, sodium salt (52166-72-0)		2,5-Dichlorophenol, potassium salt (68938-81-8)		2,5-Dichloroanisole (1984-58-3)	
Physicochemical	**Value**	**Comment**	**Value**	**Comment**	**Value**	**Comment**	**Value**	**Comment**
Melting point (°C)	59		202	EPIWIN	201	EPIWIN	21	EPIWIN
Boiling point (°C)	211						216	EPIWIN
Vapor pressure (hPa)	0.61	EPIWIN	Nil	EPIWIN	Nil	EPIWIN	0.22	EPIWIN
Partition coefficient	2.8	EPIWIN	0.12	EPIWIN	0.12	EPIWIN	3.36	EPIWIN
Water Solubility (g/L)	slightly		40	EPIWIN	34	EPIWIN	0.075	EPIWIN
Environmental fate								
Photodegradation (t1/2 days)	18	EPIWIN	1.5	EPIWIN	1.5	EPIWIN	2.0	EPIWIN
Hydrolysis	Stable	EPIWIN	Stable		Stable		Stable	
Fugacity	63.9% Soil 31.5% Water	EQCIII	55.8% Soil 44.0% Water	EQCIII	56.4% Soil 43.6% Water	EQCIII	68.8% Soil 22.4% Water	EQCIII
Biodegradability	Biodegrades		Biodegrades		Biodegrades		Biodegrades	
Ecotoxicity								
Acute Fish – LD50 (mg/L)								
Acute Daphnia – EC50 (mg/L)								
Algal Inhibition – EC50 (mg/L)								
Mammalian								
Acute – Oral (mg/kg)	2475	Rat						
Acute – Dermal (mg/kg)	>8000	Rabbit						
Acute – Inhalation (mg/m^3)	>185000	Rat						
Gene Tox – Mutagenic	negative	HGPRT Loci						
Gene Tox – *In vivo* Cytogenetic	negative	Micronucleus						
Repeat Dose – 28-day Rat, Inhalation NOAEL (mg/m^3)	100	Rat						
Repeat Dose – 21-day Rabbit, Dermal NOAEL (mg/kg-bw)	100	Rabbit						
Reproduction – NOAEL (mg/kg-bw)								
Developmental – NOAEL(mg/kg-bw)								

4.3 SIDS Matrix – Group III

SIDS Endpoint	Acifluorfen (50594-66-6)		Benzoic acid, 3-[2-chloro-4-(trifluoromethyl)phenoxy] (63734-62-3)		Benzoic acid, 3-[2-chloro-4-(trifluoromethyl)phenoxy], potassium salt (72252-48-3)		Acifluorfen, Sodium Salt (62476-59-9)	
Physicochemical	**Value**	**Comment**	**Value**	**Comment**	**Value**	**Comment**	**Value**	**Comment**
Melting point (°C)	186		146	EPIWIN	251	EPIWIN	172-176	Measured
Boiling point (°C)								
Vapor pressure (hPa)	Nil	EPIWIN	Nil	EPIWIN	Nil	EPIWIN	<1.33e-05	Measured
Partition coefficient	3.7	Measured	4.7	EPIWIN	0.56	EPIWIN	< 0.3	Measured
Water Solubility (g/L)	0.12	Measured	0.001	EPIWIN	1.9	EPIWIN	0.405	Measured
Environmental fate								
Photodegradation (t1/2 days)	3.25-4.2	Measured	5.9	EPIWIN	5.8	EPIWIN	Degrades	Measured
Hydrolysis	Stable		Stable		Stable		Stable	
Fugacity	83.8% Soil 14.1% Water	EQCIII	63.4% Soil 19.0% Water	EQCIII	41.4% Soil 58.4% Water	EQCIII	39.5% Soil 60.4% Water	EQCIII
Biodegradability	Biodegrades						Biodegrades	
Ecotoxicity								
Acute Fish – LD50 (mg/L)			> 1000				17	
Acute Daphnia – EC50 (mg/L)							77	
Algal Inhibition – EC50 (mg/L)	>260	120-hr test						
Mammalian								
Acute – Oral (mg/kg)			>50	Rat			1540	Rat
Acute – Dermal (mg/kg)			>5000	Rabbit			3680	Rabbit
Acute – Inhalation (mg/m^3)			>3400	Rat			>6910	Rat
Gene Tox – Mutagenic	Negative	Ames Assay	Negative	Ames				
Gene Tox – In-vitro Cytogenetic							Negative	Chrom Aberration
Gene Tox – In-vivo Cytogenetic							Negative	Micronucleus
Repeat Dose – 90-d Rat, Oral NOAEL (mg/kg-bw)							23.7	
Repeat Dose – 21-d Rabbit, Dermal NOAEL (mg/kg-bw)							277	
Reproduction – 2-Gen Rat, oral, NOAEL (ppm)							25 500	Parental and F1 Developmental (F2)
Developmental – Rat, oral NOAEL(mg/kg-bw)							20 180	Maternal Teratogenicity
Developmental – Rabbit, oral NOAEL(mg/kg-bw)							12 36	Maternal Teratogenicity

5.0 References

This list of references is for studies as cited in Sections 1-3, while a complete list of all data sources reviewed in the development of Robust Summaries and Test Plan for Dicamba and Acifluorfen Intermediates Category is attached as Appendix A.

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6.0 Robust Summaries

Follow Apendix A

Appendix A

This appendix contains the complete list of all data sources reviewed in the development of the Robust Summaries and Test Plan for Dicamba and Acifluorfen Intermediates Category. Reference numbers in bold indicate studies for which robust summaries have been prepared.

Reference Number	Author	Title	Source or Performing Laboratory	Year
1	Clifford Jessup D.	3-week dermal toxicity study in rabbits	International Research and Development Corporation	1980
2	Ulrich C.E.	Four-week inhalation study in rats	International Research and Development Corporation	1980
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